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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/695,559	TRYGGVASON ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☒ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *5-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-15* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/30/04, 12/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in the reply filed on December 1, 2005 is acknowledged. The traversal is on the ground(s) that the search for the other groups would overlap. This is not found persuasive because the inventions are distinct methods directed to different modes of action with different results. Furthermore, the inventions have a separate status in the art as shown by their different classifications. A method for detecting the presence of invasive cells requires a different search, than a search for a method for inhibiting tumor growth. For instance, only the method of detection requires searching for the detection of the immunocomplex and correlating the presence of the immunocomplex to the presence of the invasive cells. The methods are unrelated and provide different results. Moreover the groups related to the products have different uses and can be used with distinctly different methods. Thus the search is not extensively overlapping, like applicants assert. As such, it would be burdensome to search any combination of the inventions of Groups I-V together. The requirement is still deemed proper and is therefore made FINAL.

Specification

2. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a method for inhibiting tumor growth comprising administering to a subject with a laminin 5-secreting tumor an amount effective to inhibit tumor growth of an antibody that binds to one or more epitopes in domain III of laminin 5 γ2 chain.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.,* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the

genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. *In Gostelli*, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

The specification at page 24, para. 2 states that tumor growth inhibition in group 4 mice (mice which were administered the 5D5 antibody) relative to untreated and IgG treated mice was not statistically significant. And that Group 5 mice, which were administered the 5D5 antibody, experienced no inhibition of tumor growth. Figure 3 illustrates the lack of significant tumor growth, while Figure 4 shows only a modest decrease in the slopes of tumor growth curves in the antibody treated mice. Therefore, there is no teaching of inhibiting tumor growth. There is no teaching that the method will inhibit tumor growth in all types of subjects with a laminin 5-secreting tumor, especially since subjects can have both laminin 5-secreting tumor and non- laminin 5-secreting tumors. There are many types of cancers and carcinoma cells that do not express laminin thus the method would be ineffective at inhibiting their growth, thus the method is overbroad. Moreover, there is no teaching of administering polyclonal or monoclonal antibodies to inhibit tumor growth in cancer subjects. There is no disclosure of administering the antibody to a cancer patient. Those of ordinary skill in the art recognize the unpredictability of administering antibodies since many hurdles persist, including impaired distribution and delivery of the antibody to the carcinoma site, inadequate trafficking of potential cellular effectors to tumors, antigenic heterogeneity, shed or internalized targets, insufficient target specificity and induction of human anti-

mouse antibodies. See Weiner (Seminars Oncology, Vol. 26, No. 4, pages 41-50, 1999).

At best, the inventors can point to monoclonal antibody 5D5. However if the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. Here, applicants have not described a sufficient number of representative examples Thus one of ordinary skill in the art would not expect that the inventors were in possession of the instantly claimed invention drawn towards a method for inhibiting tumor growth comprising administering to a subject with a laminin 5-secreting tumor an amount effective to inhibit tumor growth of an antibody that binds to one or more epitopes in domain III of laminin 5 $\gamma 2$ chain.

A skilled artisan cannot envision the detailed steps of the claimed method since the specification has not defined what the method steps are. There are no examples of using the method for inhibiting tumor growth. There is no teaching of the instant method inhibiting the growth of mammary, melanoma, or colon cells. There are no *in vitro* or *in vivo* test which could correspond to the instant method being used in human cancer patients. Furthermore the art teaching that there are many shortcomings associated with extrapolating from *in vitro* to *in vivo* protocols, the problems of testing in knockout mice and problems associated with other assays. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of such a method. The written description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.").

In view of the lack of evidence in the specification as filed, it is apparent that one skilled in the art would recognize that applicants were not in possession, at the time of filing the instant application, of a method for inhibiting tumor growth comprising administering to a subject with a laminin 5-secreting tumor an amount effective to inhibit tumor growth of an antibody that binds to one or more epitopes in domain III of laminin 5 $\gamma 2$ chain. The specification does not teach a representative example from which the method is based upon. As previously stated, applicants have not shown a method for inhibiting tumor growth which is sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Thus a skilled artisan cannot envision said method and therefore conception cannot be achieved until reduction to practice has occurred. Therefore, the claims lack written description of the method. In

view of the lack of written description of the claims, the full breadth of the claims fail to meet the written description provision of 35 USC 112, first paragraph. Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention. Therefore the full breadth of the claims fails to meet the written description provision of 35 USC 112, first paragraph.

4. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabled for a method for inhibiting tumor growth comprising administering to a subject with a laminin 5-secreting tumor an amount effective to inhibit tumor growth of an antibody that binds to one or more epitopes in domain III of laminin 5 γ2 chain.

The specification fails to teach that the a method for inhibiting tumor growth comprising administering to a subject with a laminin 5-secreting tumor an amount effective to inhibit tumor growth of an antibody that binds to one or more epitopes in domain III of laminin 5 γ2 chain is equivalent to a method for decreasing tumor growth in nude mice who were administered mouse squamous cells comprising administering an antibody against γ2 chain domain III of laminin 5 to the mouse. There are no examples

of the claimed method being effective at inhibiting tumor growth in any subject with a laminin 5-secreting tumor. There is no teaching of what types of subjects the method would work in. The specification does teach the use of transgenic mice however, it should be noted that the mice are not an acceptable human model. Gura et al., (Science. 1997. Vol. 278, pages 1041-1042) disclose the shortcomings associated with testing in knockout mice and that these model systems are not predictive to the unpredictable obstacles associated with cancer treatments, furthermore, Gura et al., disclose that there are problems with extrapolating from *in vitro* to *in vivo* protocols. Thus, the instant claims are not enabled. Those of ordinary skill in the art recognize the unpredictability of administering antibodies when many hurdles persist. Weiner et al.,(Seminars Oncology, Vol. 26, No. 4, pages 41-50, 1999) teach that hurdles include the impaired distribution and delivery of the antibody to the carcinoma site, inadequate trafficking of potential cellular effectors to tumors, antigenic heterogeneity, shed or internalized targets, insufficient target specificity and induction of human anti-mouse antibodies. Thus given the unpredictability and underdeveloped art, the instant claims do not appear to be enabled. There are no working examples of using the method to inhibit tumor growth. None of these consideration have been contemplated in the specification, and in absence of these considerations, there is no assurance that the antibodies would be available in effective doses at the target sites and for the periods of time to affect the interaction of the invasive carcinomas to cause an inhibition in tumor growth.

There is no experimentation of such method, as to the quantity of experimentation needed to determine whether to method is enabled. There is no direction or guidance in the specification, and there is a complete lack of working examples. As stated above, the specification does not provide an enabling disclosure supporting the administration of an antibody against γ2 chain domain III of laminin 5 to a subject with a laminin 5-secreting tumor, wherein the administration results in the inhibition of tumor growth. Page 20 of the instant specification shows that of the SCID mice, 4 out 5 mice still had tumors. The specification at page 24, states that tumor growth inhibition statistically significant and that some mice experienced no inhibition of tumor growth. Therefore, there is no teaching of inhibiting tumor growth. There is no teaching that the method will inhibit tumor growth in all types of subjects with a laminin 5-secreting tumor, especially since subjects the SCID mice test subjects failed to have their tumor growth inhibited. In view of the lack of examples and guidance, the method is unpredictable and would require undue experimentation since a skilled artisan would be required to *de novo* determine the whether the claimed invention is enabled and the working parameters for said invention. As evidenced by Seaver (Genetic Engineering 14(14): 10 and 21, 1994) selection of a monoclonal antibody as an immunotherapeutic agent is an unpredictable task as the antibody must possess sufficient specificity and a high degree of affinity for its target for use as an immunotherapeutic agent and because these qualities are dependent on the physiology of the particular pathology and the accessibility of the target antigen (column 7, page 10 and column 3 page 21). Seaver et al., disclose many of the same hurdles as Weiner et al., above and further teach that

monoclonal antibodies made by murines will often trigger an immune response, which will result in the rapid elimination of that antibody, thereby making it ineffective as a therapeutic. Seaver et al., also state that immunocompromised nude mice are not always good candidates for nonimmunocompromised but diseased humans. See Seaver et al., Genetic Engineering News, "Monoclonal antibodies in Industry: More Difficult Than Originally thought" August 10, 1994, pages 20-21. The specification does not suggest what sort of specificity and/or affinity would be necessary for the antibodies of the claimed method so that one skilled in the art would not be able to practice the claimed invention without undue experimentation.

In absence of further guidance from Applicants, such experimentation requires ingenuity beyond that expected of one of ordinary skill in the art. Such need for non-routine experimentation demonstrates that the specification is not enabled for any asserted use or well-established use of the claimed method. The claimed method would not predictably result in an enabled method for inhibiting tumor growth. No working examples are shown containing the missing information. Without such information, one of skill in the art could not predict a method that would result in the desired method for intervention. Accordingly, one of skill in the art would be required to perform undue experimentation to inhibit a carcinoma tumor growth comprising administering to a subject with a laminin 5-secreting tumor an amount effective to inhibit tumor growth of an antibody that binds to one or more epitopes in domain III of laminin 5 $\gamma 2$ chain. Therefore, one skilled in the art could not make and/or use the invention without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Salo et al., (Acta Univ Oul.D 540).

The claims are drawn to a method for inhibiting a carcinoma tumor growth comprising administering to a subject with a laminin 5-secreting tumor an amount effective to inhibit tumor growth of an antibody that binds to one or more epitopes in domain III of laminin 5 γ2 chain.

Salo et al., (Acta Univ Oul.D 540) teach the general aspects of tumor progression wherein the hallmark of cancer cells is their ability to invade other tissues and locomote throughout the body to form new tumors (section 2.3.1). Thus a complex mix of consecutive processes of cell attachment, detachment and migration are needed for tumor progression (section 2.3.1). The authors teach that polyclonal antibodies against in domain III of laminin 5 γ2 chain inhibited migration of the mouse squamous carcinoma cells (section 6.2). Thus the authors teach that inhibition of migration inhibits tumor growth by inhibiting the necessary consecutive process. The authors made antibodies against domain III of the γ2 chain of laminin 5 (section 4.1). Thereby teaching an antibody that binds to one or more epitopes in domain III of laminin 5 γ2 chain, just as

required by the claims. Section 4.7 teaches injecting mice with mouse squamous cell carcinoma cells, KLN-205 cells (section 4.7). Then the mice were injected with antibodies against domain III of the laminin γ2 chain (anti-LNγ2-III). Salo et al., also teach targeting of polyclonal antibodies to tumors in KLN-205 mice (section 5.5). Following the inoculations of the squamous carcinoma cells, large tumors developed (section 5.5). Thus the mouse-subject had carcinoma tumors, just as required by the claims. Then anti-LNγ2-III antibody was injected in to the mice (section 5.5). Thus the authors teach administering to a subject with a laminin 5-secreting tumor an amount effective to inhibit tumor growth of an antibody that binds to one or more epitopes in domain III of laminin 5 γ2 chain, just as required by the claims.

Therefore, Salo et al., teach a method of inhibiting a carcinoma tumor growth comprising administering to a subject with a laminin 5-secreting tumor an amount effective to inhibit tumor growth of an antibody that binds to one or more epitopes in domain III of laminin 5 γ2 chain, just as instantly claimed.

Prior Art

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Giannelli et al., (1997) teach that monoclonal antibody, CM6 which binds the cleavage site of in domain III of the γ2 subunit, inhibited cell migration. Lugassy et al., teach a γ2 chain domain III of laminin 5 antibody. Salo et al., (Matrix

Biology) teach antibodies against the short arm of the γ2 chain inhibited migration of carcinoma cells.

Conclusion

7. No claims allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
February 13, 2006

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